ACUTE MYELOBLASTIC LEUKEMIA IN ITS RELATION TO PRIMARY ANEMIA.

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The following case is aptly illustrative of a type of blood disease in which the anemic and leukemic features compete for primary importance and invite critical comment.

Case History.—H. R., aged forty-six years, male, white, foundryman. Entered Halnemann Hospital November 25, 1914, complaining of extreme weakness and prostration.

The family history was negative. The patient had measles in childhood and typhoid fever at twenty-one; otherwise the past history was quite negative. He had never used alcohol, tobacco, or drugs; he was never exposed to poisons such as lead or phosphorus; he strenuously denied gonorrhea and syphilis. There was no history of tuberculosis. He was married and had six children, one dying of diphtheria.

Two or three years ago the patient had considerable trouble with decaying teeth, and had all of those in the upper and part of those in the lower jaw removed. Since then he has been wearing plates. According to various members of his family, and his own physician, the patient had been distinctly and even markedly anemic for not less than six months and possibly a year. This was evidenced by a striking yellow pallor obvious to all his relatives and friends. Six weeks before entering the hospital he scraped the skin off his left arm at the wrist, and this in a few days became infected. Carbuncle-like suppuration developed and extended a short distance up the arm, but was controlled by incision and general surgical treatment, and is now completely healed. Two weeks after the arm infection, however, the patient became so weak that he had to stop work, and his physician was impressed with the rapid increase of the anemic pallor and general illness from the time of the infection. Outside of weakness and dyspnea, dizziness or faintness on effort, the case was symptomless. There was neither gain nor loss of weight. There had never been any glandular enlargement. There was no history of hemorrhage at any time or from any place, and there was no bleeding while in the hospital.

Examination. The patient was plainly seen to be extremely anemic. The marked anemic pallor with the yellowish tinge and the fairly fleshy condition of the subject suggested pernicious anemia. The mucous membranes were very pale. Along the lower incisors and bicuspids there was pyorrhea alveolaris. At a later period an ulcerated area at the junction of the natural and false teeth on the right side developed, apparently from the rubbing of the plate;

otherwise the mouth and throat had been and remained remarkably free from scorbutic, ulcerous, gangrenous, or hemorrhagic conditions.

There were no superficial or deep glandular enlargements demonstrable during his hospital stay. The spleen gave no evidence, by palpation or percussion, of increase in size.

The heart exhibited an anemic murmur. The blood-pressure was 100 mm. systolic and 50 mm. diastolic. The lungs were negative. The abdomen was negative. There was no enlargement of the liver. Examination of the gastric contents gave free HCl, 37; total acidity, 62; no lactic acid; no occult blood. The feces showed no animal parasites and no occult blood. The urine was quite negative. The Wassermann test was negative. The neurologist reported negatively, as did the ophthalmologist on the eye-grounds. Two roentgenographic examinations gave nothing definite.

The patient was twenty-five days in the hospital when he died. He complained of weakness, but otherwise was quite comfortable and mentally keen. While in the hospital he ran a temperature of from 99° to 101° F., with occasional higher flights. His pulse was 110 to 115. The blood findings are shown in tabular form. An autopsy could not be obtained.

DISCUSSION. Ten years ago, in a suggestive article on "Acute Lymphatic Leukemia," McCrae[1] concluded: "(1) In the majority of cases of acute leukemia there is a rapid destruction of the red cells with the blood features of a severe primary anemia; (2) the essential changes in acute leukemia are in the bone-marrow; (3) in the study of future cases more attention should be paid to the changes in the red cells and the probable similarity to pernicious anemia definitely decided." He found in a review of forty cases an average color index of 0.94. In 24 out of 45 cases he found the red count below 1,500,000 and in 38 out of 45 cases below 2,500,000. He says: "Such a proportion of low counts with a high color index we find in only one other disease, namely, pernicious anemia. Does such a finding not suggest that we have with the special leukemic features also a very rapid severe anemia of the primary type?"

In studying the case herewith reported these notes of McCrae seemed especially relevant. While the red-cell findings, in acute leukemia may of themselves suggest pernicious anemia, these are, of course, at once contradicted in the very great majority of cases by a high white cell count which makes the diagnosis relatively simple. Further, glandular and splenic enlargements are common and diagnostically helpful. But glandular enlargements were absent in this patient, and with the history of chronic anemia and the blood findings of the first examination before us the diagnosis of pernicious anemia seemed justified and was made. Later the

[1] Brit. Med. Jour., 1905, i, 404.

flood of the circulation with great numbers of myeloblasts had to be considered as a terminal event or a challenge to the first diagnosis.

TABLE OF BLOOD FINDINGS.

Date of examination.	Hemoglobin, per cent.	Red cells.	Color index.	White cells.	Differential count (500 leukocytes).				Nucleated reds per c.mm.	Megaloblasts, per cent.	Normoblasts, per cent.
					Polynucleats, per cent.	Lymphocytes, per cent.	Eosinophiles, per cent.	Myeloblasts, per cent.			
Nov. 28	18	1,130,000	0.8	7,800	22.0	66.0	0.2	11.8	3,356	62	38
Dec. 5	19	820,000	1.2	12,000	32.8	30.8	0.1	36.3	3,344	56	44
Dec. 13	16	810,000	1.0	128,800	9.2	10.8	....	80.0	11,265	43	57
Dec. 14	..	....	....	132,000							
Dec. 15	..	....	....	146,000							
Dec. 16	14	865,000	0.8	163,000	9.2	3.6	....	87.2	18,207	42	58
Dec. 17	..	....	....	175,600							
Dec. 18	..	....	....	168,000							
Dec. 19	..	....	....	195,000							
Dec. 20	..	1,030,000	....	298,000	4.2	7.2	....	88.6	29,334	60	40

NOTE.—On the first examination were noted slight variations in the size and shape of the red cells and a fair number of macrocytes. There were slight polychromatophilia. The nucleated reds and polychromatophilia increased markedly with the progress of the disease but other red-cell changes were not as extreme. Blood plates were slightly reduced.

On November 28 the first blood findings of 1,130,000 red cells, a color index of 0.8, 7800 leukocytes, 66 per cent. of lymphocytes, and numerous nucleated reds with megaloblasts predominating appeared quite typical of pernicious anemia even though there were 11.8 per cent., of myeloblasts. Adding to this the absence of glandular and splenic enlargements and the history of chronic anemia the diagnosis seemed inevitable. In regard to the duration of the anemia I may say that while there was no previous blood examination I am reasonably sure from close questioning of four members of the family and the family physician that there was grave anemia without glandular enlargement for at least six months. The patient's appearance was such that he was the constant subject of inquiry and comment among his friends and relatives. The second blood examination, one week later, foreshadowed the myeloblastic invasion; and the third examination, fifteen days after the first, showed a full-fledged acute leukemia. Minus the leukocytic factor the blood was that of pernicious anemia; with it was that of leukemia. From December 13 until the day of his death, December 20, leukocyte counts and spreads were made daily and showed the progressive increase of myeloblasts together with the development of anemic changes in the red cells. In twelve days the white cells rose from 12,000 to 298,000.

The number of nucleated red cells was remarkable, reaching a maximum of 29,334 per cm. This is seldom seen except in a primary anemia and usually then in association with terminal leukocytic phenomena, as will be mentioned below. Megaloblasts predominated in some counts, normoblasts in others. Billings[2] reported a case somewhat similar to this in which the nucleated reds numbered 10,336 per cm., 7092 being megaloblasts. Solley[3] described a case of pernicious anemia with a normoblastic crisis, the nucleated red cells reaching 35,100. Grawitz[4] cited a grave anemia in a boy, aged seven years, the red count being 380,000 and the nucleated reds 10 per cent. of the total number. Brill[5] reported a pernicious anemia which after transfusion and splenectomy developed a blood picture also somewhat similar to my case, the nucleated red cells reaching the enormous number of 94,080 per cm.

If the case be adjudged pernicious anemia a terminal acute leukemia may be assumed. The above-mentioned cases of Billings, Grawitz, and Brill ended this way: Billings' case finally exhibited a leukocytosis of 34,000 with 29.4 per cent. of myelocytes, and looked like splenomyelogenous leukemia. Grawitz's patient had 55,000 leukocytes with 25 per cent. of myelocytes and 20 per cent. of large hyaline cells. Brill's case ended in what he terms an acute myeloid leukanemia with a white-cell count of 73,920, of which 21 per cent. were myelocytes and myeloblasts. Geissler and Japha[6] reported a terminal blood condition in a boy, aged six years, in which the red cells reached the extraordinarily low count of 158,000. The leukocytes were 34,000 with 90 per cent. of lymphocytes. Some authorities do not admit a terminal leukemia, but speak of an antemortem leukocytosis or lymphocytosis, and Grawitz considered his case pernicious anemia with leukocytosis. The case here reported, however, reaching a white cell count of 298,000 with 88.6 per cent. of large hyaline cells, not to be confused at all with lymphocytes, could hardly be classed otherwise than as a leukemia.

On the other hand the case may be considered leukemia throughout with severe terminal anemia. This would be acceptable if we were dealing with simply an acute leukemia, for most of the leukemias confused with pernicious anemia have been of this type. But this patient was certainly anemic at least six months, and the leukemia if present must have been of the chronic type. Chronic leukemias may, of course, terminate with the blood picture of the acute type. This occurred in Van der Wey's[7] and Wilkinson's[8]

[2] Tr. Assn. Amer. Phys., 1900, xv, 308.
[3] Reports of Presbyterian Hospital, New York, 1902, v, 189.
[4] Berl. klin. Wchnschr., 1901, xxxviii, 641.
[5] Tr. Assn. Amer. Phys., 1915, xxx.
[6] Deutsch. med. Wchnschr., 1900, xxvi, 65.
[7] Deutsch. Arch. f. klin. Med., 1896, lvii, 287.
[8] Lancet, London, 1903, i, 1739.

patients. A case of chronic myeloid leukemia I had observed for two and a half years and treated with benzol developed 54 per cent. of myeloblasts before death. Further, the low leukocyte count of the first examination is not contradictory to leukemia, for it is well known that a low count may be encountered at the beginning or end or during the course of the disease. The previous infection might explain the drop. An objection obtains here, however, which prohibits the diagnosis of chronic leukemia, and that is the entire absence of glandular or splenic enlargement. Acute leukemia may show no enlargement throughout its course, but chronic leukemias invariably present splenic or lymphatic enlargements at some time, and this patient's history is clearly contrary to this demand. Such diagnoses as aleukemia, aplastic leukemia, and atypical leukemia are likewise excluded on the same grounds, these diseases also showing splenic and glandular enlargements.

The term leukanemia makes a strong appeal for application here, implying as it does a combination of leukemic and anemic features. Von Leube's[9] original case had severe anemia, a relatively low leukocyte count (10,500), enlarged spleen, and a blood formula suitable for chronic leukemia. Most of the cases reported as leukanemia have been similar in these respects. The present case lacks the enlarged spleen and the usual blood formula. Moreover, the term seems to be rejected and denounced by so many hematologists that one hesitates to apply it. Ewing[10] speaks of it as a "term referring to a disease which may be regarded provisionally as constituting a point of union of leukemia and pernicious anemia." So regarded its application to this case is interesting. My patient's lesion, as far as clinical evidence could indicate, was in the bone-marrow and the predominant and diagnostic blood cell the myeloblast. The presence of large numbers of nucleated red cells and myelnblasts together with the significance of the myeloblast as a primitive parent marrow cell make its relation to pernicious anemia and leukemia suggestive.

Ward's[11] suggestion to classify leukemias as primary and secondary, just as anemias are spoken of as primary and secondary, is interesting. Such secondary leukemias have been described following sepsis and fractures. But the blood, as Ward points out, is never quite perfectly leukemic, just as the secondary hemolytic anemia is never as absolutely typical as a primary pernicious anemia. The case herewith reported might be classed as a secondary leukemia and accounted for by the preceding septic infection. Objections to this theory would be that the suppurative condition had healed about four weeks before the leukemic blood picture

[9] Berl. klin. Wchnschr., 1900, xxxvii, 851; also Deutsch. Klin., 1903, iii, 177.
[10] Clinical Pathology of the Blood, 1903, p. 484.
[11] Lancet, London, 1914, clxxxvi, 1459.

developed, and this blood picture was typical as far as a myeloblastic leukemia is concerned.

SUMMARY. A case of grave anemia presented in the last eight days of life a blood picture of acute myeloblastic leukemia with extraordinary numbers of nucleated red cells. The previous diseased blood condition, which had existed undoubtedly six months, is a question for debate, but there is much evidence to suggest it was pernicious anemia. The matter is interesting, as emphasized by McCrae, on account of the common association of severe anemia of the primary type with acute leukemia; and also because of the location of the lesion of both pernicious anemia and acute leukemia in the bone-marrow, together with the problem of the relation of the primitive myeloblast to the formation of red cells and leukocytes.

ON THE NATURE OF THE BACTERICIDAL PROPERTY OF VAGINAL SECRETION.

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INTRODUCTION. Döderlein, in his work published in 1892, was the first investigator to make a statement in respect to the bactericidal property of vaginal secretion. During the twenty years that have elapsed since then many attempts have been made to investigate the factors causing this bactericidal property, but none of them have thus far produced any satisfactory result.

Döderlein kept the vaginal bacillus in bouillon cultures at 37° C. for one or two days, so that they might freely develop, and he produced therein a considerable amount of lactic acid. He transplanted the staphylococcus into the culture, but was unable to discover any signs of this organism, and was thus led to conclude that the lactic acid in the vagina was the product of the vaginal bacillus and was bactericidal in nature. Years after, however, Krönig discovered experimentally that lactic acid is not the product of the vaginal bacillus alone and is not by any means the sole agent possessing bactericidal power.

He obtained unsuccessful results in the treatment of cases of pathological vaginal secretion with 1 per cent. lactic acid solution, and considered this to be another evidence that the lactic acid is not sufficiently protective against the pathogenic flora therein present.

Though Winter and Witte still entertained doubts relative to